DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Rockville MD 20857

MAY 2 2006

The Honorable Mark E. Souder
Chairman
Subcommittee on Criminal Justice,
Drug Policy and Human Resources
House Committee on Government Reform
Washington, D.C. 20515-6148

Dear Mr. Chairman:

Thank you for the letter of December 21, 2005, in which you requested that the Food and Drug Administration (FDA or the Agency) provide information and respond to several questions concerning the drug, Mifeprex (mifepristone, also known as RU-486). Below are the follow-up questions you asked after the April 3, 2006, briefing between FDA representatives and members of your staff. Your questions are repeated followed by the Agency's responses.

We would like to begin the answer to the first question by providing a brief introduction to FDA's Adverse Event Reporting System (AERS). AERS is FDA's database of post-marketing adverse event reports. It consists of data from the Spontaneous Reporting System (SRS), a forerunner of the current AERS database (for reports from 1968 to October 1997) and data from AERS (for reports from November 1997 to present). AERS is a surveillance system that relies on voluntary reporting of adverse events to FDA by health care professionals and consumers, as well as reporting (some voluntary, some required by regulation) by pharmaceutical manufacturers. It includes reports from the United States and other countries of serious adverse events, non-serious adverse events, labeled adverse events (adverse events that are listed in a drugs approved labeling), and unlabeled adverse events, as well as unlabeled adverse events attributed to a drug in post-marketing clinical trials. It generally does not contain reports from clinical trials conducted prior to the approval of a product. As of April 2006, AERS contained approximately 3.5 million reports for all drugs.

When evaluating reports from the AERS system, it is important to recognize several caveats. First, accumulated case reports cannot be used to calculate actual incidences of adverse events or estimates of risk for a product, as the reporting of adverse events is a voluntary process with inherent underreporting. Furthermore, reporting to the AERS database is influenced by other factors such as duration of marketing, market share, sales force size and sophistication, publicity about an adverse reaction, and regulatory actions. Additionally, the AERS database (as discussed below) often contains multiple reports of the same incident.

A search of the AERS database for adverse event reports received through March 31, 2006, and listing mifepristone as a possible medication retrieved a total of 1,024 reports. This total of 1,024 mifepristone reports includes duplicate reports, reports concerning the use of mifepristone unrelated to pregnancy termination (e.g., treatment of certain cancers), and reports originating outside the U.S. For the analysis in this letter, we refer to the total number of reports, prior to adjustment for duplicate reports or off-label use, as the crude number of reports. Unless otherwise specified, the following responses to your questions relate to crude numbers of reports listing mifepristone as a possible medication. In some instances, the same event in the same patient can be reported more than once because of duplicate reporting (e.g., a physician sends the report directly to FDA as well as to the company, which in turn sends the report to FDA). The collection of all reports pertaining to a single incident in a single patient is referred to as a case. For some analyses, we have indicated that data are expressed in terms of cases rather than in terms of reports.

Reponses to Specific Questions

1 (a) How many total AERs have there been associated with RU-486?

A total of 1,024 mifepristone reports have been received through March 31, 2006. Of these 1,024 post-marketing adverse event reports, after we accounted for duplicate reports, reports for use of mifepristone for indications other than termination of pregnancy, reports in men or infants, and reports from outside the U.S., there were 950 cases involving mifepristone use in the U.S. in women for termination of pregnancy.

(b) How many of those have been reported since the Dear Doctor letter of Apr. '02?

A search of the AERS database for reports received from April 17, 2002, to March 31, 2006, retrieved 941 mifepristone reports.

(c) How many have been reported since the Dear Doctor letter of Nov. '04?

A search of the AERS database for reports received from November 12, 2004, to March 31, 2006, retrieved 320 mifepristone reports.

(d) How many have been reported since the FDA public health advisory in July '05?

A search of the AERS database for reports received from July 19, 2005, to March 31, 2006, retrieved 111 mifepristone reports.

(e) How many AERs to date have involved transfusion cases?

In order to respond to this question, we manually reviewed the clinical details of the 950 cases reported to AERS and involving mifepristone use in the U.S. in women for termination of pregnancy. We identified 116 cases documenting that the patient received a blood transfusion due to heavy bleeding after medical abortion. The

Mifeprex® U.S. labeling warns about this adverse event in a **BOXED WARNING** and the **WARNINGS SECTION** as follows:

> **BOXED WARNING:**
> Bleeding. Prolonged heavy bleeding may be a sign of incomplete abortion or other complications and prompt medical or surgical intervention may be needed. Advise patients to seek immediate medical attention if they experience prolonged heavy vaginal bleeding (see WARNINGS).
>
> **WARNINGS SECTION:**
> Vaginal bleeding occurs in almost all patients during a medical abortion. Prolonged heavy bleeding (soaking through two thick full-size sanitary pads per hour for two consecutive hours) may be a sign of incomplete abortion or other complications and prompt medical or surgical intervention may be needed to prevent the development of hypovolemic shock (see BOXED WARNINGS). Patients should be counseled to seek immediate medical attention if they experience prolonged heavy vaginal bleeding following a medical abortion.
>
> According to data from the U.S. and French trials, women should expect to experience vaginal bleeding or spotting for an average of nine to 16 days, while up to 8 percent of all subjects may experience some type of bleeding for 30 days or more. Bleeding was reported to last for 69 days in one patient in the French trials. In general, the duration of bleeding and spotting increased as the duration of the pregnancy increased.
>
> Excessive vaginal bleeding usually requires treatment by uterotonics, vasoconstrictor drugs, curettage, administration of saline infusions, and/or blood transfusions. In the U.S. trials, 4.8 percent of subjects received administration of uterotonic medications and nine women (1.0 percent) received intravenous fluids. Vasoconstrictor drugs were used in 4.3 percent of all subjects in the French trials, and in 5.5 percent of women there was a decrease in hemoglobin of more than 2 g/dL. Blood transfusions were administered in one of 859 subjects in the U.S. trials and in two of 1800 subjects in the French trials. Since heavy bleeding requiring curettage occurs in about 1 percent of patients, special care should be given to patients with hemostatic disorders, hypocoagulability, or severe anemia.

2. (a) Please list all drugs have been pulled or withdrawn from the market since 1997 (see attached table for a listing of 1997-2001 drugs).

We will respond to this question shortly.

(b) List and then summarily describe the evidence, studies, and case reports that prompted FDA to conclude that the marketing approval for each drug needed to

be withdrawn (e.g., longitudinal studies demonstrating predictable events, epidemiological evidence, adverse event reports, etc.).

We will respond to this question shortly.

(c) Please indicate for each withdrawn drug whether and why FDA believed or did not believe that a causal relationship had been demonstrated between the use of the drug in question and the relevant adverse events.

We will respond to this question shortly.

(d) What constitutes sufficient epidemiological evidence for AERs to necessitate a drug's withdrawal if there is no "causal link or relationship" established between the drug and the adverse events in question?

The decision to withdraw a drug from marketing, or to withdraw the approval of a drug, is a complex decision that is based on a number of important considerations, of which potential causality is only one. Other important considerations include the severity and nature of the adverse event in question, the incidence of the event in relation to drug use, the ability to modify or predict the potential for the adverse event, and the availability of alternative treatments and their relative safety. It is also important to note that the large majority of drug withdrawals have been undertaken voluntarily by the manufacturer; the considerations and evidence that go into a manufacturer's decision to voluntarily withdraw its product may be different from those that affect FDA's decision to formally withdraw the approval for a drug through the regulatory process.

AERS reports alone would not commonly provide a sufficient basis for either FDA or sponsor action, since AERS reporting generally does not support causality assessments and does not allow for accurate assessment of the frequency of an event in relation to drug use. It is important to note, however, that there are occasions where an adverse event is simply not seen until a product is marketed, so that its reporting through AERS in temporal association with drug use leads to a high index of suspicion. One recent example would be that of rhabdomyolysis reported in association with a statin drug (used to treat high cholesterol) without the accompanying exercise or severe metabolic derangements that more commonly are associated with this unusual adverse event. Nonetheless, even in such circumstances, the Agency does not rely solely on the reports in AERS, but needs to make other assessments to try to establish event rates and dose relationships. For instance, Baycol was withdrawn (by the sponsor) in part because evidence indicated that it caused rhabdomyolysis more frequently than other statin drugs, but also because it did so at lower relative doses than similar statin drugs. These additional assessments for frequency and other important considerations usually involve the assessment of data outside of what is available through AERS reporting alone, including reconsideration of aggregate data from the pre-approval and post-approval clinical trials database, data from any large clinical trials conducted by other entities (e.g., NIH trials) and/or data from large medical claims databases (i.e., observational studies conducted by FDA or other pharmacoepidemiologists).

(e) In our discussion on Friday, FDA officials indicated that the agency places AERs into four loose analytical boxes with respect to causation. What is the typology that FDA uses to analyze drug-adverse event relationships? Please describe it. Is this typology described in any published literature or agency documents that are available to the public?

The Adverse Event Reporting System (AERS) is a complex computerized information database designed to support FDA's post-marketing safety surveillance program for all approved drug and therapeutic biologic products. The ultimate goal of AERS is to improve the public health by providing the best available tools for storing and analyzing safety reports. The example provided during your discussion was intended to help clarify a complex process for evaluating data-rich reports. For example, each report is evaluated, among other considerations, on whether or not the adverse event reported is serious, non-serious, expected or unexpected, as those terms are defined in FDA's regulations at Title 21, *Code of Federal Regulations* (CFR) 314.80.

The reports in AERS are evaluated by clinical reviewers in FDA's Center for Drug Evaluation and Research (CDER) and Center for Biologics Evaluation and Research (CBER) to detect safety signals and to monitor drug safety. They can form the basis for requesting further epidemiological studies when appropriate. The collected reports are monitored and observed for emerging patterns. In the event it appears there may be potential for a widespread product problem, the Agency will initiate action as needed.

Extensive information on AERS is publicly available, including from the following:

The FDA Adverse Events Reporting System webpage:
http://www.fda.gov/cder/aers/default.htm

Selected Regulations Related to Post-marketing Safety Reporting:

21 CFR 310.305-- Records and reports concerning adverse drug experiences on marketed prescription drugs for human use without approved new drug applications.
21 CFR 312.32 -- IND Safety Reports.
21 CFR 314.80 -- Post-marketing reporting of adverse drug experiences

International Conference on Harmonisation ICH E2B international safety reporting guidance: *http://www.fda.gov/medwatch/report/iche2b.pdf*

3. Has the FDA ever approved any other drug regimen/label that mandates the" off-label," or unapproved, use of another drug?

There are instances that the labeling for one drug recommends its use with a second drug without the approval of the sponsor of the second drug. Some examples of this are:

Herceptin, a biologic, was approved for use in Her2neu positive breast cancer "in combination with paclitaxal" for metastatic breast cancer in patients who have not been treated for their metastatic cancer with chemotherapy (i.e., as first line treatment). The randomized study supporting this use gave all patients chemotherapy, in many cases with paclitaxel, then added either Herceptin or no additional therapy to the 2 groups. It showed a clear benefit of the added Herceptin. A study of this design can detect the effect of the Herceptin but does not establish the contribution of the paclitaxel. When Bristol-Myers sought a claim for Taxol in first-line treatment of breast cancer on the basis of the Herceptin study, the claim was rejected because there was no evidence that Taxol contributed to the effect of the Taxol-Herceptin treatment. Thus, paclitaxel is recommended for use with Herceptin in Herceptin labeling for first line treatment of metastatic breast cancer, but is not itself approved for that use. The recommended use of paclitaxel with Herceptin is thus an off-label use.

There are similar examples in heart failure. Several beta blockers and ACE inhibitors are approved for use in heart failure to prevent serious outcomes (death, hospitalization for heart failure) and in all cases, use with diuretics is recommended, even though outcome effects of diuretics in heart failure have not been established and are not claimed in labeling. Carvedilol labeling, for example, indicates the drug for use, usually in addition to diuretics; digoxin, and an ACE inhibitor, to increase survival and decrease hospitalization.

4. **While the 7+ deaths received the most attention, the other 800+ AERs are also of great concern and could be very useful in identifying trends. Please provide us with all of a summary of the demographic and clinical presentation data from the adverse event reports. We would assume that the FDA has "crunched the numbers" on the AERs, so please provide a copy of the data summary that the FDA is using in monitoring this regimen. We would expect this to include at minimum a breakdown of AERs by geography (city, state), age range, ethnicity, type of adverse event (hemorrhage, infection, sepsis, etc), classification (severe, moderate, mild), outcome (death, ongoing complications, full recovery), and reporting source (state/local government, family/friend, Danco, news media).**

I. Introduction

Please refer to the response for Question No. 1 for a summary of the AERS database and issues related to the use of post-marketing data.

II. Mifepristone U.S. Post-marketing Adverse Events Summary Through 03/31/2006

The Office of Drug Safety can provide a line listing for all 1,024 mifepristone reports received through March 31, 2006. Since this line listing of all mifepristone reports is over 200 pages in length, we are providing a summary of the pertinent information for the adverse event cases below. However,

please let us know if you would like a printout of the line listings of all 1,024 mifepristone reports received through March 31, 2006.

The following information is from U.S. post-marketing reports (i.e., not from a pre-approval clinical trial) received by FDA of adverse events that occurred among patients who had taken mifepristone for medical termination of pregnancy. Because FDA has eliminated duplicate reports that we have identified, and in some cases, reclassified the adverse event terms for individual cases after reviewing the narrative details, the numbers provided here may differ from the numbers of the reports that may be obtained through Freedom of Information Act requests. These events cannot with certainty be causally attributed to mifepristone because of information gaps about patient health status, clinical management of the patient, concurrent drug use and other possible medical or surgical treatments. The estimated number of women who have used mifepristone in the U.S. through the end of March 2006 is approximately 575,000 women, according to Danco Laboratories, LLC.

Table 1 (see below) is a summary of the cumulative number of mifepristone cases and the *a priori* events and outcomes of interest received through 03/31/2006. The overwhelming majority (98.8 percent) of the 950 mifepristone cases initially were submitted by the sponsor, with only 11 reports initially received from patients, health care providers, investigators, attorneys or family members. Approximately one-quarter of the 950 patients were hospitalized and less than 1 percent of the patients died or experienced life-threatening events. The most frequently reported event of interest in the case reports was blood loss requiring a transfusion (12.2 percent of cases), followed by infection (9.3 percent) and ectopic pregnancy (2.8 percent). Approximately 40 percent of the reported 950 cases were received from 3 states, with 163 cases initially reported from California, 117 from New York, and 103 from Arizona, for a total of 383 cases. The overwhelming majority (93.8 percent) of cases occurred in women aged 18 years or older, with an average age of 27.3 years, median age of 26 years, and a reported age range of 13-46 years. Age was unspecified in 3.8 percent of reported cases.

Table 1. Post-Marketing Adverse Events in U.S. Women Receiving Mifepristone for Pregnancy Termination

Overall Summary (Cases received in AERS through 03/31/2006)		
Cumulative number of cases with any adverse event	950	
Outcomes of Interest		
	Number of Cumulative Cases	**% of Cumulative Cases**
Death	8	0.84%
Life-threatening	9	0.95%
Hospitalized, excluding fatal & life-threatening cases	232	24.4%
Events of Interest		
Experienced blood loss requiring a transfusion[1]	116	12.2%
Infection[2], including severe infection	88	9.3%
Ectopic pregnancy[3]	27	2.8%
Severe infection[4]	18	1.9%
Hypersensitivity event	16	1.7%
Thrombotic/thromboembolic event	6	0.63%
Report Source		
Sponsor (Population Council/Danco Laboratories LLC)	939	98.8%
Direct Reports	11	1.2%
Initial Report Received from: • Healthcare Providers – 2 • Attorney – 1 • Patient – 6 • Centers for Disease Control – 1 • Family – 1		

Geography – Number of Cases Received by State (based on location of initial reporter)							
CA	163	MA	26	NC	15	AK	3
NY	118	MD	24	IN	14	DE	2
AZ	103	CT	23	KS	9	GA	2
MI	48	TN	22	MO	9	LA	2
IL	45	PA	21	DC	8	AL	1
WI	45	FL	18	KY	7	MN	1
WA	42	NJ	18	RI	7	MT	1
TX	33	VT	17	NM	6		
IA	28	OR	16	HI	4		
OH	28	CO	15	VA	4	Unknown	2

[1] As stated in the mifepristone labeling, bleeding or spotting can be expected for an average of 9-16 days, and may last for up to 30 days.

[2] Not included are women with reported sexually transmitted infections such as Chlamydia infections and gonorrhea, cystitis and women with toxic shock syndrome not associated with a pelvic infection.

[3] Administration of mifepristone and misoprostol is contraindicated in patients with confirmed or suspected ectopic pregnancy (a pregnancy outside the uterus).

[4] This subset of infections includes cases that were determined to be severe based on a medical review of the case details. FDA generally considers "severe infections" to be those that involve hospitalization for at least 3 days, intravenous antibiotics for at least 24 hours, total antibiotic usage for at least 3 days, and other physical or clinical findings, laboratory data or surgery that suggest a severe infection.

Demographic Information		
Average Age (years)	27.3	
Median Age (years)	26	
Age Range (years)	13-46	
	Number of Cumulative Cases	**% of Cumulative Cases**
Age Unspecified	36 cases	3.8%
Age < 18 years	23 cases	2.4%
Age ≥ 18 years	891 cases	93.8%

Please note that the following information could not be provided:

- City: this information is not readily retrievable from the listings generated from the AERS database. Summaries by state have been provided according to the location of the initial reporter for the adverse event case.
- Ethnicity: this information is not systematically captured on the MedWatch form.
- Classification (severe, moderate, mild): this classification is not generally utilized for post-marketing data. Post-marketing data is classified by the serious outcomes listed in FDA's regulations at 21 CFR 314.80(a). These serious outcomes are captured on the MedWatch form and entered into the AERS database.
- Outcome (death, ongoing complications, full recovery): event resolution is not systematically captured on the MedWatch form, although death is captured as a serious outcome per FDA's regulations at 21 CFR 314.80(a).

5. Does the FDA have an estimate of how many doses of RU-486 have been administered? If so, how was that number determined? If the number is estimated by Danco, what does the FDA know about how Danco calculates that number?

According to Danco, the sponsor of the mifepristone application, as of March 31, 2006, there have been approximately 575,000 doses of Mifeprex administered.

- The calculation by Danco to arrive at that number is:
-

Total sales minus returns

Deduct 10 percent (amount of product they estimate people stock)

90 percent of the remaining balance and multiply by three (because the pills are packaged in packs of three, and most centers appear to have been using 200 mg of mifeprex with vaginal misoprostol instead of the approved dose of 600 mg of mifeprex).

Thank you again for contacting us concerning this matter. If we can be of further assistance, please let us know.

Sincerely,

David W. Boyer
Assistant Commissioner
for Legislation